REMARKS

Claims 56, 58, 61, 65, 70, 76, 82, 83, and 106 have been examined on the merits. The remaining claims have been canceled. Applicant's acknowledge the Examiner's acceptance to the IDS filed November 7, 2006. Claims 56, 58, 61, 65, 70, 76, 82, 83, and 106 are currently amended. Support for the amendments is found throughout the specification at, for example, paragraphs [0067]-[0071], [0089], and Example 10.

Rejections under 35 U.S.C. § 112, first paragraph

On page 2 of the Office Action mailed July 22, 2008, the Examiner rejects claims 65, 82, and 83 under 35 U.S.C. § 112, first paragraph, because "the specification, [although] being enabling for making a recombinant RSV ... having baculovirus GP64 with the recited limitations regarding stability, does not reasonably provide enablement for making any enveloped recombinant vertebrate virus with those same infectivity stability properties." Applicants traverse the rejection.

At the outset, the claims have been amended to recite baculovirus GP64 as the heterologous envelope protein of the claimed invention. At the time the instant was filed, those of ordinary skill in the art of molecular virology and molecular genetics were capable, in light of the present specification, of providing GP64 to recombinant virus in both cis and trans capacity. For example, the Examiner's attention is invited to Kumar et al., 14 Human Gene Therapy 67-77 (2003), provided herewith. The Kumar paper demonstrates that baculovirus GP64 may be used to pseudotype lentiviral vectors. More specifically, as the present specification teaches the production of GP64-carrying virus in trans, from Vero cells that express GP64, Kumar produced GP64-carrying virus in trans, from 293T cells that express GP64. *See also* [0089] of the instant application. Kumar rightly noted that "packaging cell lines based on GP64 pseudotyping can thus be ***easily created***, making the ***practical production of large amounts*** of standardized vector, enough for efficient gene transfer in *in vivo* and *ex vivo* studies." Page 68, col. 1, second full paragraph (emphasis added). Hence, at least trans expression of a recombinant, live, attenuated virus was, in light of the present specification, enabled at the time the application was filed.

Importantly, however, the Examiner should note that Kumar is absolutely silent regarding infective stability under various storage conditions. Indeed, it appears that Kumar used virus immediately following harvest. Page 68, col. 2, first full paragraph. Nevertheless, screening for the

stability of viral infectivity would not require undue experimentation for one of ordinary skill in the art in light of the present specification.

Such viruses that would benefit from the stability offered are also well-described in the instant specification. For example:

> [0067] The viruses that can be modified by the invention include those that are sensitive to freezing/thawing or unstable when stored at or above 0°C (e.g., at 4°C, room temperature, or 37°C). These viruses can be either DNA or RNA viruses. Preferably, these viruses are pathogens for humans or animals. Exemplary viruses amenable to the present invention include, but are not limited to, those selected from Pararnyxoviridae (e.g., pneumovirus, morbillivirus, or rubulavirus), Arenaviridae (e.g., arenavirus such as lymphocytic choriomeningitis virus), Bunyaviridae (e.g., phlebovirus or hantavirus), Coronaviridae (e.g., coronavirus or torovirus), Filoviridae (e.g., Ebola- like viruses), Flaviviridae (e.g., hepacivirus or flavivirus), Herpesviridae (e.g., simplexvirus, varicellovirus, cytomegalovirus, roseolovirus, or lymphocryptovirus), Orthonzyxoviridae (e.g., influenza A virus, influenza B virus, influenza C virus, or thogotovirus), Poxviridae (e.g., orthopoxvirus, avipoxvirus, or leporipoxvirus), Retroviridae (e.g., lentivirus or spumavirus), Rhabdoviridae (e.g., lyssavirus, novirhabdovirus, or vesiculovirus), and Togaviridae (e.g., alphavirus or bubivirus). Other enveloped viruses or viruses with a membrane derived from the host cell plasma membrane can be also be modified according to the invention.

> [0071] In yet another embodiment, the recombinant virus is prepared from a paramyxovirus (e.g., a parainfluenza virus type I, II, or III, a respiratory syncytial virus, a measles virus, or a mumps virus) by incorporating a heterologous envelope protein into the viral membrane. The heterologous envelope protein comprises the ectodomain of a baculovirus GP64 protein, and is capable of mediating entry of the recombinant paramyxovirus into mammalian host cells.

> [0089] For another instance, the GP64-based envelope protein can be introduced into the recombinant virus by using a transcomplementing packaging system. A packaging cell line transiently or stably transfected with the coding sequence of the GP64-based envelope protein can be used to provide the GP64-based envelope protein in trans to complement the HRSV viral cDNA which lacks one or more functional endogenous transmembrane protein genes. The recombinant virus thus obtained is not transmissible, but can be infectious due to the presence of the GP64-based envelope protein. The non-transmissibility of this recombinant HRSV provides further safety and attenuation in that the virus can only enter, replicate, and express its encoded antigens in the first cell it infects and cannot spread to other cells. This feature represents a major advantage over other known attenuated HRSVs.

The Examiner asserts, on page 4 of the Office Action, that "additional research would be needed to determine if other enveloped vertebrate viruses in combination with GP64 ... would have the stability as instantly claimed under the same storage conditions." Applicants acknowledge that

additional research would be needed, but urge that such research would not be undue. Indeed, storing recombinant virus and periodically testing its infectivity is routine to one of ordinary skill in light of the present specification. Hence, Applicants request that this § 112 rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

On page 4 of the Office Action, the Examiner rejects claims 65, 82 and 83 under 35 U.S.C. § 112, second paragraph, for being unclear regarding the meets and bounds of the term "storage conditions." Applicants traverse the rejection, but in an effort to expedite prosecution have deleted references to "storage conditions" from the claims. Example 10 of the instant application uses the phrases such as "storage at 4°C," "stored at 4°C," "storage at room temperature for six weeks," used in the context of measuring stability of the infectivity of the recombinant, live, attenuated virus. Hence, in light of the specification, one of skill in the art understands how virus is stored according to the claims.

On pages 4-5 of the Action, the Examiner rejects claim 83 as unclear for "maintaining storage temperature or temperatures above …" Applicants have deleted this language.

Hence, these § 112, second paragraph, rejections may be withdrawn.

Objections to the Claims

On page 5 of the Office Action, the Examiner rejects claim 106 for the acronym RSV SH and suggests that the claim recite "small hydrophobic" instead. Applicants have amended the claim accordingly and ask that this objection be withdrawn.

Obviousness Type Double Patenting

On page 5 of the Office Action, the Examiner rejects claims 56, 58, 70, 76 and 106 "on the ground of nonstatutory obviousness-type double patenting … over claims 1-3 of U.S. Patent No. 7,041,489 B2." Applicants traverse the rejection. Nevertheless, in an effort to expedite prosecution, a Terminal Disclaimer is filed herewith.

Rejections under 35 U.S.C. § 102(a)

The Examiner, on page 6 of the Office Action, rejects claims 56, 58, 61, 70 and 76 under 35 U.S.C. § 102(a) "as being anticipated by Wertz et al. (WO/029416 A)." Applicants traverse the

rejection. Under § 102(a), novelty is defeated, e.g., if the invention was described in a printed publication before the invention thereof by the applicant for patent. The publication date of WO/029416 A is April 10, 2003. The Examiner's attention is invited to the accompanying Declaration of Antonius G.P. Oomens, Ph.D., Under 37 C.F.R. § 1.131, and Exhibit A to that Declaration, filed herewith. In his Declaration, Doctor Oomens explains that the present invention was invented before April, 2003. In particular, for example, in an experiment that ran from November, 2002 to January, 2003, an RSV with its glycoproteins substituted with GP64 maintained its infectivity over an eight-week period when stored at 4°C. Hence, because the present invention was invented before the publication of the WO/029416 A, this reference is not available to support a § 102(a) rejection. Applicants respectfully suggest that the § 102(a) rejections be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner, on page 8 of the of the Office Action, rejects claims 56 and 61 under 35 U.S.C. § 103 "as being unpatentable over Wertz et al. (WO/029416 A) and Parrington et al. (WO 02/09749 A2)." Applicants traverse the rejection.

As established above, WO/029416 A is no longer available for either a § 102(a) or a § 103 reference. *See* MPEP § 2141.01. Turning, then, to Parrinton, the Examiner asserts that "Parrington et al., teach the storage of RSV compositions at various temperatures in order to test the stability of the virus ... *see paragraph 65.*" (Italics original.) The cited paragraph reads:

> [0065] The vaccines were assessed for stability for 42 months at 5°C, 5 months at 25°C and 5 weeks at 37°C to ensure physical and biological stability over time. Stability studies indicated that the F and G antigens in the non-adjuvanted vaccines are stable at 25°C for at least 6 weeks.

The preceding paragraph refers the reader to Example 3 for the preparation of the subunit vaccines to which [0065] refers:

> [0064] ***RSV sub-unit preparations***, produced according to Example 3, were used to formulate a non-adjuvanted vaccine, an alum-adjuvanted vaccine and a placebo control that contained only alum. The total protein present in a single dose of the vaccines of the antigens RSV F, G, and M was 100 µg, present in 0.5 mL of phosphate buffered saline. In the alum-adjuvanted vaccine, there was 1.5 mg of alum per 0.5 mL of vaccine.

Parrington's Example 3, starting at [0056], does not refer to a recombinant, live, attenuated vaccine, but teaches solublized F, G, and M proteins that are prepared in bulk from infected cells. Indeed, as recited in Parrington's [0010], "it would be desirable to identify vaccine ***components***, such as RSV ***subunit components***, that could elicit a protective immune response in the absence of extrinsic adjuvants, such as alum." (Emphasis added.) Nowhere does Parrington teach or suggest live, attenuated, recombinant virus. Moreover, there is nothing in Parrington to suggest that GP64 could be expressed in a live, attenuated, recombinant virus, and that such expression will provide stability to an otherwise labile virus. Hence, Parrington does not support a § 103 rejection. Applicants respectfully request that this § 103 rejection be withdrawn.

CONCLUSION

In view of the above elections and remarks, consideration and allowance of the instant application is respectfully requested.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 19-2380. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

Date: January 21, 2009

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